CLINICAL USE OF ANTIBIOTICS

- A Rationale

In the Service of Medical Profession

Karnataka Antibiotics & Pharmaceuticals Ltd.
(A Government of India Enterprise)
BANGALORE

THE HOUSE OF ANTIBIOTICS

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Foreword

Modern life is witnessing a series of rapid changes in every field of human endeavour with medicine in the forefront making significant strides.

The tremendous spurt of progress began with the discovery of penicillin. In the recent years pharmaceutical research has unravelled more of the mysteries of this drug and other newer anti-infective agents creating a dramatic impact by reducing the morbidity and mortality of life threatening infections. Since the toxic reactions of many drugs are ill understood, therapeutic misadventures have occurred and continue to occur at an alarming rate.

With the result it necessitates the clinician to develop more rational criteria for the use of various drugs and antibiotics.

This booklet, a KAPL's service to medical profession is intended to assist the practising physician in choosing the appropriate antibiotic. An attempt has been made to present as much concise information as possible, the topic being so vast.

While this booklet is not a substitute to the text book as a source of information, it is intended to stimulate physicians and to reinforce the rational understanding of the use of antibiotics.

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INTRODUCTION

The greatest impact of drug therapy has been in the field of infectious diseases, from the standpoint of overall morbidity and mortality.

Drugs in ancient medicine, essentially herbal, were used empirically with occasional benefits but often with disastrous consequences. Applications of mouldy breads and ingestion of fungi for Intestinal disorders are ancestors of antibiotic therapy.

Louis Pasteur's postulate on germ theory of disease and Paul Ehrlich's elucidation of magical bullets perhaps serve as the beginning of the Antibiotic era. The spurt of progress in the search for antibiotics and newer drugs began with the accidental discovery of penicillin by Sir Alexander Fleming.

Modern chemotherapy of infectious diseases dates back to mid 1930's when the sulfonamides (dye derivatives) were introduced. *Till then to kill pyogenic bacteria in the body had seemed impossible.*

Penicillin, the first systemically used antibiotic in the early 1940's, was stimulus for the search and use of effective drugs against bacteria, fungi, parasitic and rickettsial infections.

The efficacy of antimicrobial agents is due to their action in inhibiting growth of the parasite rather than to an enhancement of the body defense mechanisms. It is remarkable that such a large number of substances can interfere effectively with multiplication of invading organisms without seriously damaging the cells of the host.

Effective new agents continue to appear from large scale screening programs and also from chemical modification of known drugs.

AIMS OF THE REVIEW

1) Concise description of the antibiotics in current use.
2) Practical tips on factors influencing selection of antibiotic and outcome of therapy.
3) Do's and Don't's while handling antibiotics.

SELECTION OF ANTIMICROBIALS AND OUTCOME OF THERAPY

A. Susceptibility of Infectious Micro organisms

No antimicrobial agent is effective against all pathogenic micro-organisms. Each has its own spectrum of activity against one or a variety of species within which the majority of strains are susceptible. However, a variable percentage of strains of each susceptible species is resistant. It is customary, therefore, to determine the susceptibility of most pathogens to a variety of chemotherapeutic agents.

B. Bactericidal versus Bacteriostatic

Though used relatively, certain drugs have a primarily killing (bactericidal) action while others simply inhibit bacterial growth (bacteriostatic) assisting the defense mechanism of the host.

Bactericidal

Penicillin
Cephalosporins
Vancomycin
Polymyxins
Aminoglycosides

Bacteriostatic

Tetracycline
Sulfonamides
Chloramphenicol
Erythromycin

Clinical Pharmacology

It is imperative to know the kinetics of antibiotics to render its use effective and safe.

Details of absorption and excretion, blood and urine levels with various routes of administration, protein binding, renal clearance, half lives of drugs and stability in solutions are critical factors.

Dose, Route and Duration of Therapy

In the dosage of antimicrobials the objective is to deliver a concentration in excess of that needed to inhibit / kill the infecting organism at the site of infection. Since it is difficult to measure tissue concentrations, a blood level that exceeds the MIC two-eight fold is an accepted guideline. In UTI excess of drug in urine is obviously important.

The route of administration and dose is important in achieving appropriate drug levels.

Parenteral therapy should be reserved for severe infections in order to attain effective blood levels.

It is advisable never to administer more than one agent at a time by the IV route.

IV administration is specially indicated in meningitis, endocarditis and osteomyelitis to overcome barriers of penetration with high blood levels.

IM injections are acceptable as an alternative and offer prolonged and effective blood levels with antibiotics like procaine penicillin.

The oral route is used for mild to moderate infections and to complete therapy for severe infections brought under control with parenteral therapy.

The optimal duration of antimicrobial treatment varies. But, as a general rule it is necessary to continue therapy for 2-3 days after the temperature has returned to normal and all signs of infection have subsided.

Allergy & Toxicity

Always explore the allergic history before prescribing any antimicrobial. The use of skin test in identification of penicillin allergy is useful. Alternative antibiotics are available for any switch over if need be.

Drug toxicity related to renal function is of particular importance. Drugs like Penicillin, Cephalosporin. Chloramphenicol, Erythromycin and Lincomycin are relatively safe at normal or slightly reduced dosage in the presence of renal impairment.

Aminoglycoside dosages have to be reduced based on serum creatnine levels and toxic agents like Tetracycline. Streptomycin, Sulfonamides and Nitrofurans are best avoided.

Site of Infection

Soft tissue infection in sites with good blood supply and minimal necrosis are in general easily treated.

Penetration of antimicrobials could pose a formidable problem in meningitis and endocarditis and lead to treatment failure. Penetration across the blood brain barrier is a complex phenomenon involving protein binding, lipid solubility and ionisation.

Foreign bodies, abscesses and obstructions interfere with response to chemotherapy and usually prevent cure until they are removed, drained or relieved.

Combination Therapy

Most bacterial infections can be treated with a single antimicrobial agent once the etiological agent is recognised. Combination therapy is used to broaden the antibacterial spectrum while awaiting the results of culture and also cover the possibility of mixed infections.

True synergism occurs between penicillin and streptomycin against a number of gram positive and gram negative pathogens.

Antagonism occurs when bacteriostatic drugs are combined with bactericidal agents.

Superinfection - Resistance

A number of micro organisms are genetically resistant to clinically feasible levels of antimicrobials and obviously will not be affected by antibiotic therapy.

Most antibiotics alter the hosts' normal flora by removing organisms sensitive to the drug. While in most cases this ecological change is of little consequence, occasionally the commensal bacteria of the host sets up infection - ***superinfection.*** The super-infecting organism is ***resistant*** to the drug being administered and determining its sensitivity - susceptibility is helpful in selecting the most appropriate antibiotic. Some superinfecting organisms develop resistance to multiple drugs by a plasmid mediated Resistance factor. Specially multiple drug resistant E.coli, Klebsiella and Enterobacter pose a particular problem to hospitalized patients.

ANTIBIOTICS

Definition:

Antibiotics are chemical substances elaborated by various species of micro-organisms such as fungi, actinomycetes and bacteria, which suppress the growth of other micro-organisms and may ultimately destroy them.

Most antibiotics are obtained from fungi, but some like Bacitracin, Colistin and Polymyxin B are obtained from bacteria. Certain are entirely synthesised by chemical methods e.g. Chloramphenicol.

Classification

While there are 2 primary ways of classifying antibiotics, one based on the Mechanism of Action and the other on Antibacterial Spectrum, the former is given below.

A. Drugs that Inhibit bacterial cell wall

Ex: Betalactams: Penicillin and Cephalosporins:

B. Drugs that affect cell membrane permeability

Ex: Antifungals: Nystatin and Amphotericin B

C. Drugs that affect Bacterial Ribosome (50'S') sub unit

Ex: Chloramphenicol, Erythromycin and Tetracyclines.

D. Drugs that bind to 30'S' Ribosomal sub unit

Ex. Aminoglycosides- Streptomycin and Gentamicin

E. Agents that affect Nucleic acid metabolism

Ex: Rifampicin, Nalidixic acid, Metronidazole and Quinolones.

PENICILLIN & RELATED ANTIBIOTICS

BETALACTAMS

Penicillin was the first antibiotic introduced into clinical use way back in 1939. The recent developments include a new class of agents; the ureidopenicillins and the development of Beta lactamase resistant penicillins. The various Beta lactams are listed below.

BETA LACTAMASE ANTIBIOTICS

A. PENICILLINS

1. **Natural Penicillins** (Beta lactamase susceptible)	Benzyl penicillin Benzathine penicillin Procaine penicillin Phenoxy ethyl penicillin }oral Phenoxy methylpenicillin}
2. **Extended Spectrum Penicillins**	Ampicillin-Amoxycillin
a) Aminopenicillin (Aminogroup side chain)	Bacampicillin Cyclacillin and Hetacillin
b) Anti Pseudomonas Penicillin	a) Carboxypenicillin Carbenicillin, Ticarcillin b) Ureidopenicillin Azlocillin, Mezlocillin Piperacillin & Aptacillin
3) **Beta lactamase Resistant Penicillin** (Anti Staph penicillin)	Methicillin Nafcillin, Oxacillin Cloxacillin and Dicloxacillin
4) **Other Penicillins** (Anti Gram negative Penicillin)	Amidinocillins, Temocillin

5) Combination with Beta lactamase inhibitors (Combination with 2 A & B will further broaden the spectrum)	Amoxycillin + Clavulunate Ticarcillin + Clavulunate Ampicillin + Sulbactam Ampicillin + Cloxacillin

B. CEPHALOSPORINS

1) First generation	Cefazolin
2) Second generation	Cefoxitin, Cefuroxime
3) Third Generation	Ceftriaxone and Ceftazidime

C. PENEMS

Imipenem with cilastatin

D. MONOBACTAMS

Aztreonam.

NATURAL PENICILLINS

Penicillin G with a benzyl side chain to the basic Beta lactam ring is the most active natural penicillin. Penicillin G is short acting since it is rapidly excreted by the kidneys. Various modifications have been made to prolong the action of Penicillin G, with these preparations being administered by the deep intramuscular route. Peak levels of these preparations are always lower than with Penicillin G but is high enough to inhibit susceptible bacteria. Once bactericidal levels are reached, the therapeutic concentration is maintained for long periods.

Penicillin G, administered orally is destroyed by the gastric juice before it reaches the site of maximal absorption in the duodenum. In mild infections where oral penicillin is used, it is best given 1 hour prior to a meal to minimise inactivation and to prevent delay in absorption. Penicillin G orally is unpredictable in serious infections that necessitates large IV doses of 12 - 24 millions units per day.

Penicillin G is strongly bound to plasma proteins, which serves as a circulating depot releasing the antibiotic into circulation.

Penicillin G penetrates the inflamed meninges and joint spaces but fails to penetrate the infected eyes.

Penicillin G is excreted almost unchanged by the Kidneys, making renal function crucial to prevent accumulation. Probenicid delays excretion by competing for renal tubular secretion leading to maintenance of high blood levels for long periods - a necessity in treating infections.

Antibacterial activity

Penicillin G is one of the most potent antimicrobial agents that inhibits the growth of susceptible organisms in a concentration as low as 1 in 50 million.

Penicillin G is effective against Gram positive and Gram negative cocci and some Gram positive bacilli. Gram negative bacilli are usually resistant.

Majority of Streptococci except Enterococci are susceptible.

Staphylococci initially highly sensitive have acquired resistance on a large scale.

Gonococci, Pneumococci Meningococci are highly sensitive.

Bacillus anthracis, Corynebacterium diptheriae and most Clostridium species are highly sensitive.

Treponema pallidum are extremely sensitive to penicillin.

Mech of Action

Penicillin G is a bactericidal drug that acts against actively multiplying organisms by interfering with cell wall synthesis of bacteria.

Preparations and Dosage

1) Penicillin - Benzyl penicillin - sodium & potassium salts:
   Injection 500.000 units/ml

2) Benzyl penicillin Tablet: 50.000-500.000 units
   Dose: 200.000 - 400.000 units 4th hourly
   Peak levels: 0.2 - 0.3 units/ml in 1 - 2 hours.

3) Procaine Benzyl penicillin - Powder
   Dose: 500.000 - to 1.000.000 units daily Intramuscular
   Peak levels: 0.3 units/ml in 1-3 hours

4) Fortified Benzyl Penicillin
   300.000 units of procaine benzyl penicillin plus 100.000 units of Benzyl Penicillin
   Serum levels for over 12-24 hours.

5) Procaine Penicillin in oil with 2% Aluminium monosterate (PAM)
   Serum levels for over 72 hours.

6) Benzathine Penicillin (Penidure)
   Dibenzyl ethylene diamine salt of Benzyl penicillin
   Dose: 600.000 - 2.400.000 units
   Peak levels: 0.03 - 0.1 units/ml
   - persisting levels for 10 days
   1.2 million units - persisting levels for 3 weeks.

Adverse Reactions

Remarkably safe drug but for the risk of Anaphylaxis.

G.I.T: Oral use - Nausea and vomiting

Local: Sterile inflammatory reaction, local pain erythema and Induration

INTRAVENOUS: Thrombophlebitis

CNS: Convulsions - anxiety and mental disturbances

INTOLERANCE: Idiosyncratic, anaphylactic and allergic reactions may occur.

Risk of Reaction on Parenteral administration

5 - 10% Benzathine penicillin

2 - 5% Procaine Penicillin

1 - 3% Benzyl penicillin

Mortality in severe reactions 9 - 13 %

Anaphylaxis occurs in 0.1% patients

Allergic manifestations include:

1) Skin rashes with pruritus
2) Serum sickness like syndrome with rash, fever, eosinophilia, Lymphadenopathy, angioneurotic oedema, asthma and arthralgia,
3) Positive coomb's test
4) Anaphylaxis - Acute cardiovascular collapse, bronchospasm and angioedema.

Skin tests for penicillin allergy can often prevent potentially serious anaphylaxis.

JARISH HERXHEIMER REACTION:

Rare reaction reported in patients of syphilis treated with penicillin - who show an initial exacerbation of lesions owing to release of an endotoxin from destroyed spirochetes.

SUPER INFECTION:

Use of penicillin may suppress the bacterial flora and encourage superinfection by organisms Klebsiella, Aerobacter, Candida and Pseudomonas.

HYPERKALEMIA:

Potassium salts of penicillin may increase potassium levels in patients with impaired renal function.

SEMI SYNTHETIC PENICILLINS

The disadvantages of penicillin in terms of

a) Acid lability
b) Short duration of action and poor penetration
c) Narrow spectrum of activity against Gram positive organisms.
d) Inactivation by bacterial penicillinase, Development of resistant staphylococci and finally,
e) the risk of anaphylaxis

have to a certain extent been offset by the development of semi-synthetic penicillins.

Semisynthetic penicillins can be classified as

1) **Acid Resistant**
Potassium phenoxymethyl Penicillin
Potassium phenoxyethyl Penicillin and Azidocillin

2) **Penicillinase Resistant penicillins**
Anti staphylococcal penicillin
Methicillin, Cloxacillin and Dicloxacillin

3) **Effective against Gram positive and Gram negative organisms**
Ampicillin, Amoxycillin and Carbenicillin

ACID RESISTANT PENICILLINS

Penicillin V (Phenoxymethyl) is an acid stable compound that shares the same spectrum of activity but attains 2 - 5 times higher plasma levels than Benzyl penicillin.

About 50 - 70 % of penicillin V is plasma protein bound and around 25% is excreted in urine.

Preparations

Phenoxymethyl penicillin
65 - 125mg (125mg equal to 200.000 units)
Dose: 250 - 500mg every 4 - 8 hours

Oral Penicillin V is used in mild infections requiring prolonged treatment. It has no place in severe infections or in Meningitis, Syphilis or Actinomycosis.

PENICILLINASE RESISTANT PENICILLINS

The basic 4 membered Beta lactam ring of penicillins are disrupted by enzymes penicillinase or Beta lactamase present in the periplasmic space between cell wall and cell membrane of certain Gram negative bacteria. These enzymes are encoded in the bacterial chromosome or the DNA present in plasmids.

Two options exist in the fight against the beta lactamase enzymes

a) Inhibition of Beta lactamase enzymes
b) Modify the drug to resist enzyme action

CLOXACILLIN - DICLOXACILLIN

Cloxacillin is an Isoxazolyl penicillin or Penicillinase resistant penicillin which has an acyl side chain that protects the Beta lactam ring from inactivation by the enzyme Beta lactamase. Cloxacillin is stable in acidic medium, adequately absorbed after oral use and is specially indicated for infections with Staphylococcus.

The anti staphylococcal penicillins are potent inhibitors of the growth of most penicillinase producing staphylococci at concentrations of 0.05 - 0.8 mcg/litre. They are less active against micro-organisms susceptible to penicillin and not useful against Gram negative bacteria.

Administered orally, these drugs are 30 - 80% absorbed (better on empty stomach) with peak concentrations of 5 - 10 mcg reached in 1 hour. The bio availability ranges from 43% owing to Plasma protein binding of 90 - 95%. Half life ranges from 30 - 60 mins and 75% excretion is completed in 6 hours time.

CLOXACILLIN

Category

Anti Staphylococcal - penicillinase resistant penicillin.
Predominant action on Beta lactamase producing Staphylococci.
Inhibits cell wall synthesis and prevents the action of Beta lactamase.

Spectrum

Beta lactamase producing Staphylococci and other Gram positive organisms.
Not useful against Gram negative bacteria.

Kinetics

Rapid but incomplete absorption 30-80%.
Better absorbed on empty stomach.
Peak concentration of 5-10 mcg/ml in plasma in 1 hour.
Oral bio availability of - 43%
Plasma binding - 90 - 95%
Plasma half life - 30 - 60 mins
Excretion - 75%. Kidney in 6 hours after oral use.
Also present in Enterohepatic circulation.

Indications

Staphylococcal infections

Contra indications

Allergy to Penicillin

Adverse reactions

Allergic Skin rashes, Diarrhoea

Interactions

Cloxacillin in combination with ampicillin produces a wider spectrum of antibacterial activity.

Dose:

Oral 250 - 500mg 4 times daily
Parenteral 250mg IM 4 times daily
500mg IV 4 times daily slowly
Children: 50 - 100mg/kg 4 times daily.

NAFCILLIN

Nafcillin has shown better activity against staphylococcus than cloxacillin and oxacillin. Orally Nafcillin is incompletely absorbed but yields good plasma levels intramuscularly. 87% of the drug is plasma protein bound and is excreted in bile.

Dosage

Adults 250 - 500mg 4 times daily
Children 25mg/kg twice daily

EXTENDED SPECTRUM PENICILLINS

Ampicillin and Amoxycillin are aminopenicillins with extended spectrum of activity against Gram positive and Gram negative organisms. Both drugs are more effective than penicillin G in infections caused by Gram negative species such as Haemophilus influenzae, E.coli, Salmonella, Shigella and indole negative Proteus mirabilis.

Ampicillin and Amoxycillin are inactivated by penicillinase and therefore ineffective against staphylococci. Bacteria can develop resistance in the case of Salmonella, Shigella, E.coli and Proteus.

Amoxycillin is more rapidly and completely absorbed than Ampicillin, reaches higher blood levels, and is excreted in the urine in larger amounts for longer periods. Hence Amoxycillin may be more effective for the treatment of certain systemic and Urinary tract infections. Amoxycillin does not alter the bacterial flora and therefore reduces the risk of antibiotic induced diarrhoea and the emergence of antibiotic resistant Enteric bacteria.

Talampicillin and Pivampicillin are inactive esters of ampicillin hydrolysed in the intestine to release ampicillin into circulation.

AMPICILLIN

Category

An Amino Penicillin with broad spectrum bactericidal action.

Acid stable but Beta lactamase sensitive.

Inhibits cell wall synthesis.

Spectrum

Gram positive organisms and Gram negative organisms such as Haemophilus, E.coli Salmonella, Shigella and Proteus Mirabilis.

Beta lactamase destroys activity.
Ineffective against Staphylococci.

Kinetics

Orally absorbed.
Peak concentration 3 Mcg/ml after 2 hours.
Oral bio availability 62 %
Urinary excretion 82% in 6 hours.
Plasma binding 18% (Reduced in Cirrhosis and Pregnancy)
Plasma half life 1.3 hours
Probenicid delays urinary excretion.

Indications

Respiratory tract infections, Bacterial Meningitis - Septicaemia, Infective Endocarditis Urinary tract infections and Enteric fever.

Contra indications

Allergy to Penicillin

Adverse reactions

Allergic Skin rashes - Maculopapular, Diarrhoea - colitis & superinfections

Interactions

Food interferes with absorption

Dosage

Adults	250/500/1G every 6 hourly - oral
Children:	50 - 200mg/kg/day in 4 divided doses
Parenteral:	25 - 50mg/kg in 4 divided doses.
Gonorrhoea:	3.5 G + Probenicid.

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AMOXYCILLIN

Category

An Amino penicillin with broad spectrum bactericidal action.
Acid stable, Beta lactamase sensitive.
Inhibits cell wall synthesis.

Spectrum

Both Gram positive and Gram negative organisms. Haemophilus, E.coli, Salmonella and Shigella.
Ineffective against Staphylococci and destroyed by Beta lactamase.

Kinetics

More rapidly and completely absorbed than Ampicillin.
Food does not interfere with absorption.
Peak concentration 2½ times more than Ampicillin.
4 mcg/ml in 2 hours with 250mg dose.
Oral bio availability 93%
Urinary excretion - 50% in 6 - 8hrs
Plasma binding - 18%
Rapid distribution except into C.S.F.
Probenicid delays urinary excretion.

Indications

- Upper and Lower Respiratory tract infections
- Urinary tract infections
- Bacterial meningitis - Enteric fever
- Septicaemia - Infective Endocarditis
- Gonorrhoea - Urethritis

Contra indications

Penicillin allergy.

Adverse reaction:

Well tolerated - Diarrhoea less frequent.
Allergic Skin rashes.

Dosage

Adults:	250 - 500mg every 8 hourly
Children	20 - 50mg/kg/day in 3 divided doses
Parenteral:	50 - 100mg/kg/day IM in 3 divided doses
Gonorrhoea:	3 G + Probenicid

CARBOXY PENICILLINS

These drugs have extended spectrum of action like Ampicillin, but have carboxy side chain instead of Amino group.

Spectrum

Carbenicillin is specially active against Pseudomonas, Indole positive Proteus and Enterobacter.

Not active against Klebsiella.

MIC for pseudomonas 75 - 100mcg/ml.

Higher blood levels are achieved because of increased stability and lower renal clearance.

Many patients with Gram negative infections have renal impairment and do well with 10 - 15 gr of carbenicillin.

Concomitant administration of Aminoglycoside gentamicin with carbenicillin delays the development of resistance and produces synergistic action.

Carbenicillin Indanylsodium is stable in gastric acid and reaches exceptionally high levels in the urine and may be used as a safe, effective and convenient antibiotic in recurrent UTI and prostatitis.

Ticarcillin is another semisynthetic penicillin useful against Pseudomonas infections which is 4 times more effective than carbenicillin.

CARBENICILLIN

Category

Semisynthetic penicillin with carboxy side chain
Effective against Pseudomonas.
Bactericidal action by cell wall synthesis inhibition.

Spectrum

Specially active against Pseudomonas, Indole positive Proteus and Entero bacter.
Not active against Penicillinase producing organisms.
MIC level of 0.1 - 32 mcg/ml.

Kinetics

Not absorbed orally
Parenteral administration: Intramuscular - Intravenous.
- 1 G IVly MIC -> 20 - 30 mcg/ml after 1 hour
- 2 G IVly MIC -> 47 mcg/ml after 1 hour
- 1 G IVly MIC -> 70 - 140 mcg/ml after 15 mins
- 5 G IVly MIC -> 300 mcg/ml after 15 mins
- 24 - 30 G IV Infusion MIC -> 100 mcg/ml over 24 hours.

Plasma half life 1 - 15 hours (Increased in renal failure)
Plasma protein binding - 50%
Primarily excreted by kidney - 80% in 4 - 6 hours.
Probenicid prolongs serum concentrations and delays excretion.

Indications

Pseudomonas infections of Respiratory and Urinary tract.
Systemic infections with Proteus.

Contra Indications

Allergy to Penicillin

Adverse Reactions

Local pain at the injection site, Thrombophlebitis, Purpura and Haemorrhage.
Electrolyte disturbances: Hypokalemia - Hypernatriemia following large doses.

Caution

Avoid in Patients with congestive cardiac failure and in those who need sodium restriction.

Interactions

Gentamicin has synergistic action with Carbenicillin and delays development of resistance.

Combination of Gentamicin and carbenicillin are incompatible and should be administered separately.

Dosage

Severe Systemic infections -

Adults: 20 - 30 Gram in divided doses every 4 - 6 hours
Administer infusion over 3 - 4 mins slowly
Urinary tract injections: 4 - 8 Grams daily IM

Children: 50 - 100 mg/kg body weight IM
250 - 500 mg/kg daily IV.

REDUCE DOSAGE IN RENAL IMPAIRMENT

FOURTH GENERATION PENICILLIN

The **Ureidopenicilins** are broad spectrum antibiotics:

- **Mezlocillin, Azlocillin and Piperacillin**

Spectrum

Gram negative bacilli specially against Klebsiella, Proteus, Escherichia coli.

Inactive against most Staphylococci.

Use

Proven suspected pseudomonas infections.

Broad spectrum coverage of infections.

Advantages

Lower sodium load

Less frequent hypokalemia

Reduced platelet dysfunction

Minimal need for dosage adjustment

Wider antibacterial spectrum

PIPERACILLIN

Category

Broad spectrum, 4th Generation, Ureidopencillin which is a piperazine derivative that has bactericidal action by cell wall inhibition.

Spectrum

Wide range of Gram negative organisms including Klebsiella, Pseudomonas and Enterobacter.

More active than Carbenicillin against Pseudomonas.

Kinetics

Not absorbed orally.

Intramuscularly well absorbed.

Kinetics is Dose dependent.

Peak plasma levels 30 - 40 mcg/ml in 30 - 50 minutes.

Plasma protein binding 20%.

Plasma half life - 1 hour (Prolonged in neonates and in renal failure)

Primarily excreted by Kidney 60-80% in 24 hours

Also excreted by bile - 25%

Probenicid delays excretion and enhances concentration.

Indications

Proven or suspected Pseudomonas infections of bone, joints - soft tissue, respiratory, urinary tract and pelvic and intra abdominal organs.

Synergistic action with Gentamicin in severe life threatening infections.

Contra indications

Mild infections and history of Penicillin allergy.

Adverse Reactions

Allergic skin reaction, Gastro intestinal disturbances, thrombophlebitis. Local pain at the injection site, Eosinophilia, transient elevation of Liver enzymes.

Much less Hypokalemia and Hypernatriemia than Carbenicillin.

Caution

Incompatible with aminoglycosides, metronidazole and betalactams. Never combine, always use separately.

Interactions

Synergistic bactericidal action in combination with gentamicin and beta lactamase agents.

Dosage

Adults: 3 - 4 G Average 4 - 8 hourly IVly.
Maximum dose of 24 G daily.
Slow IV infusion over 3-5 minutes.
Intramuscularly - Not to exceed 2G single dose

Children: 100-300 mg/kg in divided doses

REDUCE DOSAGE IN RENAL FAILURE.

INDICATIONS FOR PENICILLIN

Useful against infections caused by

1) Streptococcus pneumoniae, Beta haemolytic streptococci, Strep viridans, Micro aerophilic, Aerolin streptococci and Bacteriodes
2) Gonococcal and Meningococcal infections
3) Long term prophylaxis of Streptococcal sore throat to prevent reinfection in patients with Rheumatic fever to prevent development of R.H.D.
4) Infective Endocarditis - Most organisms except Enterococcus are sensitive. High intravenous doses are required.
   In Enterococcal infections high intravenous does are requried.
   Penicillins can be combined with Gentamicin/Streptomycin.
5) Pneumococcal Pneumonia - IM Procaine Penicillin - seven days to prevent relapse.
6) Meningococcal meningitis
   100.000 - 300.000 units of Cryst.Peni 4 - 6 hourly.

7) Gonorrhoea & Syphilis:
   4.8 mega units of penicillin G + probenicid
   2.4 mega units of benzathine - primary/sec symptoms
   Oral Ampicillin or Amoxycillin and Tetracycline in Gonorrhoea and Urethritis.
   3G of Amoxycillin on 1st day OR
   3.5G of Ampicillin on 1st day, *followed by*
   2G of Tetracyclines in 4 divided doses for 7 days.

8) Staphylococcal Infections:
   All strains are susceptible against penicillinase resistant drugs.
   IV therapy with Methicillin.
   Later by oral cloxacillin.

AMPICILLIN & AMOXYCILLIN Special Indications:

Otitis Media

H influenzae, Gram negative inhabitant of throat between 3 months and 3 years invades ears. Most useful in otitis media and in preventing complications.

G.I. INFECTIONS

Salmonella typhi and parathyphi:
Eradicates carrier state.
Kills the organisms in the Gall bladder

ADVERSE REACTIONS

Hypersensitivity, Diarrhoea, Phlebitis, Super infections.
Platelet aggregation impaired.
Bleeding time prolonged with carbenicillin and Ticarcillin

DRUG INTERACTIONS

1. Bacteriostatic drugs - Tetracyclines reduces the efficacy of penicillins.
2. Penicillin and Ampicillin reduce the effectiveness of oral contraceptives - may lead to Breakthrough bleeding and unwanted pregnancy.
3. Do not mix carbenicillin and gentamicin in the same syringe - complex form renders Gentamicin ineffective.

ALTERNATES TO PENICILLIN

THE CEPHALOSPORINS

The Cephalosporins differ from Penicillins in having a six membered dihydro thiazine ring instead of five membered thiazolidine ring fused to the Beta lactam ring.

There is no true cross allergenicity and patients allergic to penicillin can be treated with the cephalosporins.

Like Penicillins, the Cephalosporins are bactericidal and inhibit bacterial cell wall synthesis. Modifications of the side chains influences pharmacological properties and antimicrobial activity.

The wide classification of cephalosporins is based on

1) Antimicrobial activity
2) Metabolic stability and
3) Resistance to bacterial enzymatic inactivation

Spectrum

Most bacteria susceptible to penicillins are also susceptible to cephalosporins including group A Strepto cocci, Viridans Streptococci, Pneumococci, Penicillin sensitive and resistant Staph aureus, Nisseria, Clostridia, Actinomycetes and Corynebacterium.

Gram negative organisms: E.coli, Proteus, Klebsiella, Shigella and Salmonella are susceptible.

FIRST GENERATION

1) **Cephalexin** Oral 1 - 4G/daily
2) **Cefazolin** IM/IV 1 - 6G/daily
3) **Cepharadine** IM/IV 2 - 8G/daily
4) **Cephaloridine** IM 2G 6 - 8 hourly

Highly active against Streptococci and Pneumococci

Moderately active against Gram negative bacilli; E.coli and Proteus

Not active against Strep feacalis and Pseudomonas

Used in UTI/Resp/Skin and Soft tissue infections - as 2nd line of agents.

CEPHALEXIN

Category

First generation Cephalosporin that is orally bactericidal against broad spectrum of organisms.
Acts by cell well synthesis inhibition.

Spectrum

Gram positive and Gram negative organisms
Streptococci, Staphylococci, Nisseria and E.coli
Not active against Pseudomonas, Strep feacalis, Proteus, Enterobacter and Haemophilus.

Kinetics

Acid Stable - orally well absorbed.
Reaches peak in about 1 hr after administration.
Dose dependent kinetics.
500mg - Plasma concentration of 18 mcg/ml
Plasma protein binding 15%

Crosses Placenta and present in breast milk
Not metabolised in the body.
Plasma half life of 1.5 - hours
Primarily excreted by the kidneys - 80% in 6 hours
Probenicid delays excretion
Also present in Enterohepatic circulation.

Indications

1st generation, orally administered for infections of Respiratory tract and Urinary tract infections.
Not useful in severe infections.

Contra indications

Allergy to cephalosporins and in Renal impairment.
Avoid in pregnancy.

Adverse effects

GIT - Nausea, vomiting, diarrhoea, abdominal discomfort
Allergic skin rashes, eosinophilia, neutropenia and Super infection with Candida.

Interactions

Food delays absorption.
Cholesterol lowering drugs may delay absorption.
(use 1 hour before or 4 hours after a meal.)

SECOND GENERATION

1. **Cefaclor**:
   Oral 750mg - 4 G 4 - 8 hours
2. **Cefamandole**:
   IM/IV 1.5 - 12G/daily 4 - 8 hours in divided dose
3. **Cefoxitin sodium**:
   IM/IV 3 - 12G/day 4 - 8 hours in divided doses
4. **Cefuroxime sodium**:
   IM/IV 750mg - 1.5G every 8 hours

Spectrum:

Wide spectrum of action - Resistant Beta lactamase
Gram negative cocci specially Klebsiella, E.coli and Proteus
Alternate to Aminoglycosides
Cefoxitin is useful in mixed infections of the G.I.T.
Cefuroxime is effective against:

1) Meningitis - H influenzae resistant to Ampicillin
2) Peritonitis in patients with End stage renal disease on C.A.P-D (continuous ambulatory peritoneal dialysis.)

CEFACLOR

Category

Second generation Cephalosporin.
Orally bactericidal by cell wall synthesis inhibition.

Spectrum

Gram positive and Gram negative organisms. Greater activity against Haemophilus; Beta lactamase producing strains.
Not active against Pseudomonas, Proteus and Enterobacter.

Kinetics

Well absorbed orally, Food delays absorption.
Dose dependent Kinetics -

250 - 500mg dose - produces peak levels of 6-13 mcg/ml at the end of ½ to 1 hour.
Plasma half life of 30 mins - 1 hour
Widely distributed in the body
Plasma proteins binding - 20%
Crosses Placenta and present in breast milk
Excreted by the kidney - 85% present in Urine.
Probenicid delays excretion.

Indications

Upper and Lower Respiratory tract infections Urinary tract infections - cystitis and Pyelonephritis skin, soft tissue infections and Gonorrhoea.

Adverse Effects

Allergic skin rashes, pruritis.
G I Symptoms of Nausea, vomiting and diarrhoea.

Contra indications

History of cephalosporin allergy

Caution

Transient elevation of Liver enzymes.
Cross sensitivity with penicillin.
Avoid in pregnant and nursing mothers
Reduce dosage in Renal failure.

Interactions

Along with Amino glycosides - Nephrotoxicity
Along with diuretics - Nephrotoxic
Food delays absorption of cefaclor

Dosage

Adults:	250 - 500mg orally every 8 hours
Children:	20-40mg/kg/1 day in divided doses (Not to exceed 1 G daily)

THIRD GENERATION

1) **Cefoperazone**
   IM/IV 2 - 12 G (6 - 8 Hours)
2) **Cefotaxime**
   IM/IV 2 - 12 G (4 - 6 Hours)
3) **Ceftizoxime**
   IM/IV 2 - 12 G (6 - 8 Hours)

- Remarkable activity and apparent safety
- Effective against Gram negative bacilli
- Resistant to Beta lactamase inactivation
- Effective in Gram negative bacterieamia of all grades of severity - UTI, Abdominal and Pelvic infections
- Surgical prophylaxis - colorectal surgery
- Bacterial meningitis

CEFOTAXIME

Category

Third Generation Cephalosporin of choice in severe bacterial infections.

A cell wall inhibiting bactericidal drug.

Spectrum

Broad Spectrum, resists Beta lactamase

Greater activity against Gram Negative organisms.
Enterobacter, E.coli, Klebsiella, Proteus, Salmonella and Shigella are susceptible.

Kinetics

Not absorbed orally. Well absorbed parenterally.
Dose dependent kinetics.

Intramuscular injections yields peak levels of 11.9 and 25.3 mcg/ml after 30 min of 500mg and 1 G dose respectively.

IV doses yields dose dependent peak levels.
Plasma half life of 1 hour (increased in neonates and in Renal failure)
Plasma protein binding - 40%
Widely distributed in the body and in C.S.F.
Crosses placenta and is present in breast milk.
Excreted by the kidneys 40-60% in 24 hours
Also present in bile 20%
Probenicid delays excretion and increases plasma levels.

Indications

Severe infections - Meningitis Septicaemia, Peritonitis. Genito urinary and Respiratory tract infections.

Contra indications

Cephalosporin allergy.

Adverse effects

Allergic skin rashes, Phlebitis, diarrhoea and Super infection with Candida.
Leucopenia, Eosinophilia and Resistance.

Caution

Reduce dosage in Renal failure.

Interactions

Azlocillin and Mezlocillin increase plasma half life of Cefotaxmine.
Interacts with theophylline and produces toxicity.
Amino glycoside and Beta lactams have synergistic action.

Dosage

Adults:	2-12 Gr in divided doses as IV infusion over 20-60 minutes
Children:	100-150mg/kg/daily
Neonates:	50-100mg/kg/daily

Adverse effects - Cephalosporins

Safest of antibiotics - Hypersensitivity, Eosinophilia, fever and drug eruptions.
Decreased platelet count - bleeding tendency
Mild reversible elevation of Liver enzymes
Antabuse reaction and Super infection

Interactions - Cephalosporins

1) Cephalosporins + Bacterio static drug - Reduced effectiveness.
2) Probenicid + Cephalosporins - toxic levels
3) Cephalosporins + Aminoglycosides or loop diuretics - Nephrotoxicity.

MACROLIDE ANTIBIOTICS

"Macrolides are useful alternates to penicillin against susceptible organisms specially Gram positive cocci like Streptococci.

In penicillin sensitive patients it may be used for the prophylaxis of Endocarditis and in the treatment of syphilis. It has found special use in Legionnaire's disease and in Enteritis due to Campylobacter."

ERYTHROMYCIN

Erythromycin is a macrolide antibiotic - primarily bacteriostatic which acts by interfering with bacterial protein synthesis, by binding with bacterial 50 'S' Ribosome subunit.

Spectrum

Gram positive bacteria
Strep pyogenes, Strep pneumoniae
Nisseria, Haemophilus, Clostridium
Treponema and Bacteriodes
Mycoplasma pneumoniae and Legionella pneumophilla

Kinetics

Acid stable - ethyl succinate salt better absorbed in fasting state.
Stearate form absorbed with meals
Peak levels:
0.3 - 0.5 mcg/ml - 250mg - 4 hours
0.3 - 1.9 mcg/ml - 500mg - 4 hours
Plasma protein binding 65 - 90%
Crosses Placenta - Present in breast milk
Elimination 1/2 life - 1.9 - 2.1 hours
Stearate - 6.6hrs
Metabolised in the liver.
Excreted in bile

Indications

Upper and Lower Respiratory tract infections.
Skin and Soft tissue infections
Diphtheria, Pertusis - Otitis media
Legionnaire's and Chancroids

Contra indications

Hyper sensitivity to Erythromycin.

Adverse reactions

Gastro intestinal side effects - Nausea, vomiting, diarrhoea.
Super infections - Photo sensitivity reactions.
Reversible deafness - Hepatotoxicity and
Cholestatic jaundice.

Caution

Patients with impaired liver functions, in renal failure and Porphyria.

Interactions

Erythromycin potentiates the action of carbamazepine, cyclosporin, Theophylline and warfarin by enzyme inhibition.
Food delays absorption of Erythromycin.

Dosage

Adults:	1-4 G daily in divided doses
Children:	30-50mg/kg in divided doses

ROXITHROMYCIN

Acid stable, newer macrolide with dosage convenience and superior kinetics.

Spectrum

Similar spectrum as Erythromycin, but better penetration and action against Streptococci, Staphylococci, Chlamydia and Mycoplasma.

Kinetics

Acid stable, well absorbed following oral administration.
Dose dependent kinetics.
Wide distribution with high tissue concentration.
Plasma half life of 10 hours (increased in Renal failure)
Primarily metabolised and excreted in feaces - 53%)

Indications

Upper and Lower Respiratory tract infections, Chlamydial infections, Atypical pneumonia and Non gonococcal urethritis.

Contra indications

Allergy to Erythromycin

Adverse Reaction

Well tolerated - Allergic skin rashes. GI upsets - Less liver damage, than Erythromycin.

Caution

Not safe in pregnancy
Interactions:
Interacts with Ergot alkaloids.
Does not inhibit hepatic enzymes

Dosage

Adults:	150 - 300mg in two divided doses
Children:	2.5-5mg/kg/daily in 2 divided doses.

BROAD SPECTRUM ANTIBIOTICS

TETRACYCLINES:

These are broad spectrum bacteriostatic agents that act by inhibiting protein synthesis by binding with the 30 's' Ribosome sub unit.

Tetracyclines are widely used against Gram positive and Gram negative bacteria and other microorganisms such as Mycoplasma, Rickettsia and Chlamydia.

The use of these agents has now become restricted owing to limitations that include

1. Appearance of resistant strains - Streptococi and Pneumococci.
2. Primary bacteriostatic action
3. Occurrence of Hepatotoxicity with high blood levels
4. High incidence of Super infections
5. Side effects like nausea, diarrhoea and photo sensitivity.

Despite these limitations, the Tetracyclines are still widely used for Respiratory , Urinary, Soft tissue and Renal infections.

The Tetracyclines are generally concentrated in bile and excreted unchanged in Urine and faeces. They also readily cross the placenta barrier and are excreted in milk. They have a special affinity for teeth and bones and are therefore contraindicated in 2nd and 3rd trimesters of pregnancy and in children below 8 years of age.

TETRACYCLINE USES

1. Broad spectrum antibiotics commonly used for respiratory and urinary tract infections with sensitive organisms.
2. Drug of first choice in Lymphogranuloma venerum and Trachoma 500mg QID.

3. Doxycycline - Minocycline as alternatives to penicillin in Gonorrhoea and Syphilis 500mg QID 7 - 14 days.

Adverse effects

1. GIT: Abdominal discomfort, Nausea and vomiting
2. Teeth: Yellow discoloration of teeth
3. Liver: Fatty degeneration in patients with renal failure and in pregnancy
4. Superinfection - with Candida albicans

Drug Interactions

1. Tetracycline + Digoxin: Tetracycline increases the bio availability of Digoxin leading to Digoxin toxicity.
2. Tetracycline + Methoxyflurane: Increases the renal toxicity of the anesthetic
3. Tetracycline + oral contraceptives: Reduced efficiency of oral contraceptives - leading to contraceptive failure.

Preparations

Tetracycline
1M - 250MG OD
IV - 250 - 500MG BD
Oral 1 - 2 gr in divided doses

Demeclocycline
Oral 600mg BD - QID

Minocycline IV/oral
200mg initially
100mg every 12 hours.

Doxycycline
IV/oral 200mg initially, 100mg daily.

DO's and DON'T's

Use Tetracyclines on empty stomach with plenty of water. Doxycycline and Minocycline may be taken with food.

Do not use with milk products or iron preparations to avoid complex formation and inadequate absorption.

Do not use out dated or degraded Tetracycline.

Advice your patient to report in case of:

1. Severe vomiting - abdominal pain or diarrhoea
2. Extreme thirst or frequent urination
3. Yellowing of skin and eyes
4. Pregnancy.

DOXYCYCLINE

Category

A long acting, bacteriostatic broad spectrum Tetracycline that acts by inhibiting bacterial protein synthesis by binding with the 50 'S' Ribosomal sub unit.

Spectrum

Broad spectrum action against both Gram positive and Gram negative organisms and other organisms like Rickettsiae, Mycoplasma, and Chlamydia.

Kinetics

Complete absorption orally (95%). Food does not interfere.
Bio availability - 93%.
Peak levels after 200mg dose is 2.6 mcg/ml after 2 hours.
Widely distributed in the body.
Crosses placenta and is present in breast milk.
Plasma protein binding 80-95%.

Excreted by faeces and urine.
Concentrated in enterohepatic circulation.
Elimination Half life is 12 - 22 hours.

Indications

Upper and lower respiratory tract infection,
Genito-urinary infections, Skin and soft tissue infection and Acne Vulgaris.

Contra indications

Tetracycline hyper sensitivity.
Pregnancy.
Children below 12 yrs
and in S.L.E.

Adverse Reactions

Gastrointestinal
Allergic rashes, Urticaria
and photosensitivity.

Interactions

Antacids and Iron Chelate Tetracyclines.
Interacts with Phenytoin, Phenobarbitone and Carbamazepine.

Dosage

200mg initial dose
100mg daily for 7 days

CHLORAMPHENICOL

Broad spectrum bacteriostatic antibiotic that acts by inhibiting protein synthesis by binding with the 50's Ribosomal subunit in susceptible organisms. While the spectrum is as broad as Tetracyclines the use is limited owing to its potential lethal toxicity. The risk of aplastic anaemia (1- in 25,000) has restricted use and frequent blood counts to detect early signs of bone marrow depression are mandatory.

Chloramphenicol is readily absorbed from the G.I.T and is widely distributed. It crosses placenta and is present in milk. Chloramphenicol is inactivated in the liver by a conjugation reaction requiring Glucoronyl Transferase. This enzyme is deficient in the liver of neonates in whom chloramphenicol is contraindicated.

Uses of Chloramphenicol:

1. Drug of choice in the treatment of Typhoid fever
2. Excellent alternate to penicillin in Haemophilus and Klebsiella infections.
3. Effective against Bacillus fragilis in life threatening peritonitis, septicaemia and post abortal sepsis.
4. Alternate to Tetracycline in Lymphogranuloma Venerum in pregnant women with poor renal function.

Adverse effects

1. Bone marrow depression - Watch for decreased counts once in 2 days.
2. Gray - baby syndrome: Inability of new born to conjugate Chloramphenicol.
3. Hypersensitivity - peripheral neuritis
4. Superinfection

Drug Interactions

1. Chloramphenicol inhibits metabolism of Dicuomarol, phenytoin. Phenobarbitone, Tolbulamide and other drugs - increasing toxicity.

2. Response of bone marrow to Iron and vitamin B_{12} altered by chloramphenicol.
3. Along with Penicillin - Chloramphenicol decreases effectiveness of penicillins.

DO's AND DON'T's

1. Take capsules on empty stomach with plenty of water.
2. Inform in case of sore throat, fever, unusual bleeding, numbness, tingling.
3. Inform in case of pregnancy
4. Avoid in children under 12 years
5. Avoid in patients with S.L.E.

Chloramphenicol

1. Palmitate:
   Oral 50 - 100 mg/kg - 6 hourly doses
2. Chloramphenicol sodium succinate:
   IV 50 - 100mg/kg 6 hourly doses

AMINOGLYCOSIDES

Aminosugars joined in glycoside linkage to hexose nucleus - constitute Aminoglycosides - which have antibacterial activity in slightly alkaline medium. They exert bactericidal action by inhibiting protein synthesis by binding with the 30's ribosomal sub unit. All agents of this group have similar antibacterial spectrum, are not absorbed orally, excreted by glomerular filtration and have toxicity on the ears and kidneys. Bacterial resistance readily develops within 2-3 days and cross resistance is observed. Aminoglycosides exhibit synergism with Beta lactam antibiotics.

STREPTOMYCIN

Streptomycin, one of the first systemic antibiotics in use since 1940's has now been widely used in Triple drug regimes for treating Tuberculosis. Along with penicillin it is used to treat Streptococcal viridans endocarditis and some Enterococcal infections.

Toxicity

Vestibular nerve toxicity, rashes, fever, contact dermatitis, pancytopenia, anaphylaxis and renal irritation.

Streptomycin sulphate IM 1 - 2 G daily OD/BD.
Other Aminoglycosides in clinical use include
Gentamicin
Neomycin
Kanamycin
Netilmicin
Paramomycin and
Amikacin

Neomycin

Aminoglycoside, broad spectrum bactericidal agent useful as an Intestinal antiseptic or locally as cream, not used systemi-

cally owing to its toxicity. The chief use of Neomycin is as an Intestinal antiseptic in hepatic precoma or prior to bowel surgery. It may be used locally as skin cream with other drugs.

It is administered orally at 4-8 Gram doses and as 5 mg skin cream.

Paramomycin

Intestinal amoebicidal and chronic bacillary dysentery, 4 G initial dose followed by 2 G in divided doses.

Netilmicin and Amikacin are semisynthetic aminoglycosides useful against a broad spectrum of organisms causing life threatening infections in Immuno-compromised individuals. Both these agents are used parenterally for severe infections and produce much less ototoxicity and nephrotoxicity. The safety margin of Amikacin is higher than Gentamicin.

GENTAMICIN

Category

An aminoglycoside antibiotic that interferes with 30 'S' bacterial Ribosomes and blocks protein synthesis.

Spectrum

Bactericidal action against Gram negative: Campylobacter, Citrobacter, Enterobacter, Klebsiella, Escherichia, Proteus, Pseudomonas and Serratia

Gram positive: Staph aureus and Listeria.

Kinetics

Poorly absorbed orally - Rapidly absorbed parenterally.
Peak levels of 4 mcg/ml after 1mg/kg dose in 30-60 mins.
Wide distribution in the body, crosses placental barrier.
Plasma half life 2 - 3 hours (increased in neonates and in renal failure)

Primarily excreted by kidney-70% in 24 hours.
Accumulation in the body - specially kidney.
Accounts for detection up to 20 days after therapy has been stopped.
Concentrated in Urine - 100mcg/ml.

Indications

Septicaemia, Neonatal sepsis - caused by Gram negative organisms.
- Treatment and prophylaxis of Endocarditis.
As combination for Pseudomonas, Enterococcal and mixed infections.

Contra indications

Hyper sensitivity to Aminoglycosides

Adverse Reactions

Vestibular damage, Nephrotoxicity, Neuromuscular blockade, Respiratory depression, Anaemia, Purpura, Convulsions and visual disturbances.

Caution

Withdraw at first sign of ototoxicity and Nephrotoxicity.
Reduce dosage is Renal impairment
Do not combine with Neuro muscular blockers.
Do not combine in same syringe/bottle with penicillin, Ampicillin and Carbenicillin
Do not use locally to prevent resistance.

Interactions

Synergism with Beta lactams - Carbenicillin, Ticarcillin and Piperacillin - (used separately)
Combination with diuretics - Nephrotoxicity.

Dosage

Adults: 3-5mg/kg in divided doses
Children: 5-7.5 mg/kg in divided doses

Limit duration of treatment from 7-10 days.

MISCELLANEOUS ANTIBIOTICS

CLINDAMYCIN AND LINOCOMYCIN

As alternates to penicillin, these agents are not the first choice for any infection. They are effective in treating infections caused by Bacteriodes and microbes resistant to other agents including methicillin resistant staphylococci. Bacteriodes cause peritonitis and abscesses when they spill into the abdominal cavity following rupture of appendix.

Diarrhoea and pseudo membranous enterocolitis are the most serious adverse effects of these drugs.

POLYMYXIN AND COLISTIN

They are active against Gram negative bacteria including Pseudomonas and are used in resistant cases. Both these drugs cause severe kidney damage.

BACITRACIN

It is mainly useful against Gram positive cocci and is used topically in combination with polymyxin or colistin for the treatment of skin infections.

MONOLACTAMS

Monolactams or Mono cyclic Beta lactam have a single Beta lactam ring structure in contrast to penicillins and cephalosporins.

AZTREONAM, a monolactam is useful in Gram negative aerobic infections and along with the aminoglycosides is useful against serious pseudomonas infections.Aztreonam is resistant to Beta lactamase producing organisms.

Administered parenterally, Aztreonam is well absorbed and reaches peak levels in 2 hours. It is 56% protein bound, crosses placenta and is present in milk. It is primarily excreted by the kidneys 60-70%.

Adverse effects include allergic skin rashes and G.I. side effects. Phlebitis following IV administration and pseudomembranous colitis are other risks.

Dosage modification is required in Renal failure and Aztreonam interacts with oral anticoagulants.

Aztreonam is used as slow IV infusion or deep IM injection of 1-8G in divided doses every 6 - 12 hours.

Single 1 G dose IV is useful in Gonorrhoea.

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QUINOLONE ANTIBACTERIALS

The Quinolone Carboxylic acids are a group of synthetic antibacterial agents structurally related to Nalidixic acid.

Nalidixic acid in use since 1963, is active against Gram negative bacteria and reached bactericidal concentration in urine to be useful in urinary tract infections.

Interest in Nalidixic acid with structural modification to the basic nucleus led us to Quinolones with action against both Gram positive and Gram negative organisms including resistors like Pseudomonas.

The Quinolones are totally unrelated to the existing antibiotics and offer clinical advantages in terms of reasonable efficacy in the absence of plasmid mediated resistance, making them reach very near the ***perfect antibacterial***.

Examples of Quinolones:

Norfloxacin,
Ciprofloxacin,
Enoxacin
Ofloxacin and
Pefloxacillin.

These agents are classified as

Systemic: Ciprofloxacin and Enoxacin
Nonsystemic: Norfloxacin.

Among the Fluoro Quinolones - Ciprofloxacin has greater activity, rare resistance in vitro, adequate pharmacokinetics and excellent clinical efficacy, making it a *benchmark* when comparing fluoroquinolones.

CIPROFLOXACIN

Category

Bench mark Fluoroquinolone - Rapidly bactericidal with unique action on DNA Gyrase.

Inhibits both A & B subunits of DNA Gyrase.

Spectrum

Broad spectrum action against both Gram positive and Gram negative organisms.
Highly effective against all uropathogens including Gonococci, Penicillinase resistant Staphylococci.
Enterobacter Pseudomonas and Haemophilus, are sensitive.
Not active against anaerobes.

Kinetics

Rapid absorption orally.
Reaches peak serum concentrations of
1.51 - 2.77mg/litre with a 500mg dose after 1 hour.
Bio availability of 50-85%.
Widely distributed in the body.
Metabolised in the liver.
Eliminated by the Kidneys 65%.
Plasma half life of 4 hours
Crosses placenta and is present in breast milk.

Indications

Urinary tract, Respiratory tract infections.
Enteric infections, Bone & joint infections.
Skin & Soft tissue infections
and Sexually transmitted disease.

Contra indications

Hyper sensitivity to Quinolones.
Pregnancy and Lactation
Children below 18 yrs of age.

Adverse Reactions

Usually mild and transient.
GI side effects: Nausea, vomiting, diarrhoea.
Skin rashes, pruritis, photo sensitivity.
Dizziness, headache, confusion & convulsions.

Caution

In patients with convulsions, cerebral arteriosclerosis and renal impairment.

Interaction

Increases Serum theophylline levels.
Antacids reduce absorption
Synergism with carbenicillin against Pseudomonas.
Synergism with H_2 blockers in Campylobacter infection.

Dosage

Adult: 250-750mg twice daily.
Severe infection: 5-10mg/kg/daily divided doses
Treatment duration: 5 - 7 days.

(Dosage adjustment required in renal failure.)

NOT RECOMMENDED FOR CHIDLREN.

OFLOXACIN

Category

New generation Fluoro Quinolone,
Broad Spectrum bactericidal action by inhibition of bacterial DNA Gyrase.

Spectrum

Gram Negative and Gram positive organisms.
Highly effective against Nisseria, Chlamydia, uropathogens, Enterobacter, Salmonella and Mycobacteria.

Kinetics

Rapid complete absorption orally.
Peak distribution into most tissues
Plasma half life of 5 - 7.5 hours.
Excreted unchanged by the kidneys
Crosses placental barrier and present in breast milk.

Indications

Respiratory tract infections, Cystic fibrosis.
Urinary tract infections.
Gonorrhoea, Urethritis.
Skin & soft tissue infections.
Bone and joint infections.
Typhoid fever and obstetrical infections.

Contra indications

Hyper sensitivity.
Pregnancy and lactation.
Children under 18 years.

Adverse Reactions

Increased Intracranial pressure, headache, visual disturbances, tremor, and restlessness.
Nausea, vomiting and diarrhoea.
Flatulence, pruritis, vaginitis, fatigue and decreased appetite.

Caution

In patients with convulsions and cerebrovascular disease.

Interactions

Decreased absorption by Antacids, minerals, iron and vitamins.
Increased Theophylline levels - Toxicity
GABA receptor inhibition.

Dosage

200 - 400mg twice daily.
Duration of treatment 10 days.
NOT RECOMMENDED FOR CHIDLREN.

RATIONALE

In the Indian market, there are more than 25 brands of Ampicillin, 20 brands of Amoxycillin, 15 brands of Quinolones and equal number of Cephalosporins. A random look at our prescriptions in the pharmacies reveals an increasing trend towards Cephalosporins and Quinolones being prescribed.

Is this because more organisms are becoming resistant to penicillins?

OR

Is it an indiscriminate prescribing trend?

There are many common trivial infections which are still sensitive to penicillins and the penicillins merit the first choice. The dosage used and the duration of therapy must be adequate to minimise the development of resistant strains.

Other antibiotics should be used only in the treatment of individuals hyper sensitive to penicillins or when the causative organism is penicillin resistant.

Most bacterial infections can be treated with a single agent once the causative organism is recognised. *(one bug: one drug).* ***While combination therapy broadens the spectrum, true synergism is clinically difficult to demonstrate. Antagonistic comibinations often lead to therapeutic misadventures.***

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Dear Doctor,

We have pleasure in presenting this booklet "Clinical use of Antibiotics - *A Rationale*" in service to the Medical profession. We would appreciate your suggestions/observations, which would immensely encourage us to serve you better.

		Please Tick (✔)
Presentation	1. Very Good	☐
	2. Good	☐
	3. Needs improvement	☐
Matter/Contents	1. Very useful & informative	☐
	2. Useful	☐
	3. Too preliminary	☐
Reference Value	1. Long term use; Shall preserve it	☐
	2. Just for casual reading	☐
	3. Not much use	☐

Suggestion for improvement

_____

_____

_____

Doctors Name _____

Address _____

_____

_____ PIN _____

Date: Signature of the Doctor

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